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Ferguson's Principle and the Prediction of Fatal Drug Levels in Blood

L. A. King

Home Office Forensic Science Laboratory, Audby Lane, Wetherby, West Yorkshire LS22 4DN, UK

1 The median fatal concentrations (EC_{50}) of various types of drugs are shown to be determined solely by their aqueous solubilities (S). Among the test substances, EC_{50} values show a range of 2000-fold, whereas the ratio EC_{50}/S is essentially constant. This behaviour is typical of 'Ferguson substances', and enables the fatal toxicity of other (depressant) drugs and related compounds to be calculated.
2 The mean relative saturation (EC_{50}/S) is 0.006, a value which shows that humans are more sensitive to narcotic agents than are the lower animals.
3 The Ferguson principle provides a broad framework for quantitative structure–activity relations in fatal drug toxicity. The empirical Hansch equation can be derived from the same thermodynamic concept of free energy which underlies the Ferguson principle.

Introduction

Many drugs exert their therapeutic effects by specific mechanisms which may involve, for example, chemical interaction with a receptor or the inhibition of an enzyme either competitively or non-competitively. For some substances, particularly hypnotics and volatile anaesthetics, it is now generally accepted that their efficacy is a direct consequence of their lipid solubility; the finer molecular features are, in themselves, of little importance. Such drugs are thought to act by disrupting physiological processes in the lipoprotein membranes of the brain. The fatal drug toxicity of these non-specific substances is likewise regarded as an extension of their normal therapeutic properties. Thus, among the barbiturate drugs, there is a high correlation between lipid solubility, as measured by P, the n-octanol/water partition coefficient, and various measures of fatal toxicity in both animals and humans (Moffat & Sullivan, 1981; King & Moffat, 1983).

However, there is now some evidence that many other drugs associated with fatal poisoning also owe their lethal properties to this non-specific mechanism. Thus when drugs are arranged in order of their index of fatal toxicity in humans, the dominant molecular features to emerge are that (lipophilic) aliphatic side-

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chains have a significantly higher occurrence among the most toxic drugs, whereas (hydrophilic) hydroxyl groups have a very high association with the least toxic drugs (L. A. King, unpublished work).

If an examination is made of fatal drug concentrations in humans then, apart from isolated exceptions (e.g. the homologous oxybarbiturates), no simple relation can be discerned with any aspect of molecular structure. However, it was pointed out many years ago (Ferguson, 1951) that the proper approach to the interpretation of narcotic levels was to consider their relative saturation and not the concentration. This hypothesis arose from the thermodynamic principles which govern equilibrium between immiscible phases. The functions of interest are the thermodynamic or chemical potential and the closely related concept of activity (see **Appendix**). In a system of two or more phases at equilibrium, the chemical potential (μ) is the same in all phases. In ideal solutions, the activity of the solute is given by the ratio C/C_o where C is the actual concentration, and C_o is the concentration of its saturated solution both expressed in mole fractions. According to the Ferguson principle, non-specific drugs produce quantitatively similar effects when present at similar relative saturations, i.e. at similar activities. According to Ferguson (1951), 'The argument may be put in a perhaps more convincing form. The meaning of the statement that certain substances exert the same narcotic effect at the same thermodynamic activity is essentially this, that the same amount of work is gained in bringing one molecule of any one of these pure substances contained in a reagent bottle on the shelf to its place in the vital phase of the narcotized organism.'

Although originally applied to volatile insecticides, this postulate has since been substantiated with hypnotics, anaesthetics and many simple organic compounds under a variety of experimental conditions in organisms as diverse as tadpoles, grain weevils and man. The effect provides a quantitative understanding of anaesthesia whether induced by volatile liquids (e.g. diethyl ether) or inert gases (e.g. xenon). The majority of investigations into non-specific narcosis has involved sublethal situations; none has included fatal drug toxicity in humans.

Procedure

Saturated solutions of drugs were prepared by dissolving the unionized species in 1M-Tris (2-amino-2-hydroxymethylpropane-1,3-diol) hydrochloric acid buffer at pH 7.5, 25°C. For the basic drugs, suitable dilutions were made in 0.05M-sulphuric acid. Quantitation was achieved by using ultraviolet (UV) absorbance spectrometry with $E1\%,1$ cm values obtained from various sources. For the two barbiturate drugs, dilutions were prepared in pH 7.5 buffer; corrections were made for the degree of ionization at pH 7.5 based on the assumption that the unionized species has zero absorbance at 239 nm. The solubilities of diethyl ether, chloroform and paraldehyde are taken from Lange (1967). The solubility of ethanol is simply the concentration of a pure solution (density = 0.788 g/ml).

Data on fatal blood levels of drugs and other toxicants were derived from Stead & Moffat (1983). For dextropropoxyphene and chlorpromazine, insuffi-

cient data were present in this latter compilation, and values were obtained from the Registry of Human Toxicology (Gomm, 1983). The EC_{50} level was chosen as the most appropriate concentration; it is defined as the median blood concentration found in fatal cases involving that drug. For dextropropoxyphene, all of the fatal population involved cases of concomitant paracetamol ingestion.

Results and discussion

The solubility data(S), EC_{50} and E1%,1 cm absorbance values are presented in Table 1. In addition, Table 1 shows the relative saturations, i.e. EC_{50}/S. It will be seen, that although there is a 2000-fold variation in EC_{50}, the relative saturation values show only a small variation. Bearing in mind the experimental uncertainties, particularly in the EC_{50} values, as well as deviations from ideal behaviour, the data are consistent with the hypothesis that, in fatal poisonings in humans, these compounds act as 'Ferguson substances'. Among the solid drugs listed in Table 1 only amitriptyline has an anomalously low value of relative saturation. The solubility of amitriptyline has been confirmed by analysis of a further sample of the drug obtained from a different source. Since the EC_{50} value (3.3 μg/ml) is unlikely to be in serious error in view of the large population of amitriptyline deaths ($n = 96$), it is possible that this drug may exert an additional and specific toxic effect causing EC_{50} to occur at about 50% of the expected value. The similarly low values of EC_{50}/S for chloroform and paraldehyde could

Table 1 Median fatal levels of drugs and related compounds in blood and their relative saturation with respect to solubility in aqueous 1M-Tris buffer, pH 7.5, 25°C

Drug	n[a]	*E1%,1 cm (λ nm)*[b]	*EC_{50} (μg/ml)*	*Solubility (μg/ml)*	*Relative saturation EC_{50}/S*
Amitriptyline	96	504 (239)	3.3	1.1×10^3	0.0030
Chlormethiazole	22	292 (258)	50.0	7.2×10^3	0.0069
Chloroform	6	—	30.0	8.2×10^3	0.0037
Chlorpromazine	19	1025 (255)	2.0	2.9×10^2	0.0069
Dextropropoxyphene	85	12 (257)	2.8	4.3×10^2	0.0065
Diethyl ether	5	—	500.0	7.5×10^4	0.0067
Dothiepin	28	108 (303)	5.2	8.3×10^2	0.0063
Ethanol	122	—	4000.0	7.9×10^5	0.0051
Maprotiline	6	63 (270)	5.0	6.4×10^2	0.0078
Paraldehyde	9	—	200.0	6.0×10^4	0.0033
Phenobarbitone[c]	51	452 (239)	45.0	6.0×10^3	0.0075
Quinalbarbitone[c]	45	393 (239)	17.0	2.1×10^3	0.0081

[a] n is number of cases used to determine median fatal concentration (EC_{50})

[b] Absorbance values used in determining drug solubility are shown because of the variability in $E1\%,1$ cm values in the literature. Thus, for chlorpromazine, if a value of $E1\%,1$ cm = 980 is preferred, then the calculated solubility is (2.9) (1025/980) $\times 10^2$, i.e. 3.0×10^2 μg/ml

[c] For the barbiturates, pK_a (quinalbarbitone) = 7.9; pK_a (phenobarbitone) = 7.4

be a reflection of uncertainties in the EC_{50} data which are based on very small populations.

Although relative saturations (EC_{50}/S) depend on the conditions under which drug solubility is determined, the unweighted mean value (± one standard deviation), i.e. $EC_{50}/S = 0.006$ (± 0.0018) is a constant characteristic of human poisoning by non-specific depressants. This value is much less than is required to produce narcosis in the lower animals (Ferguson, 1951), and suggests that humans are far more sensitive to the effects of narcotic agents.

It is a straightforward matter to calculate the median fatal concentration of any compound on the assumption that it is a Ferguson substance. Thus $EC_{50} = (0.006)S$ where S is the solubility of the compound under the conditions described.

Table 2 shows the predicted EC_{50} values of several drugs for which only limited details of fatal levels are known. For both desipramine and nortriptyline, the levels are over twice the EC_{50} values of the parent molecules (imipramine and amitriptyline respectively): a result entirely in accord with the general principles of drug detoxication.

The concept of chemical potential and relative saturation cannot be applied to 'non-narcotic' poisons which exert their lethal effects by very specific mechanisms. Thus carbon monoxide, hydrogen cyanide, paracetamol and organophosphoric acids for example, are 'non-Ferguson substances'. A second limitation to this approach arises with drugs which have a very high lipid solubility, i.e. *n*-octanol/water partition coefficient > 1000. Such compounds are unlikely to have depressant properties since they will rapidly accumulate in the first accessible lipoidal depot after administration, and will be unable to reach the brain in significant concentrations. This effect explains the biological unreactivity of saturated long-chain hydrocarbons. By definition, substances that have no lipid solubility are also non-Ferguson substances. For drugs that are rapidly metabolized, e.g. flurazepam, calculated values of EC_{50} (see Table 2) may not be wholly reliable if the metabolites have a very different solubility from the parent molecule. However, in the great majority of acute fatal poisonings, only limited metabolic conversion occurs.

It appears that the Ferguson principle may have a wider applicability than the Hansch equation (Hansch & Leo, 1979) to the study of quantitative structure–activity relations in fatal drug toxicity. Indeed, it is possible to derive the empirical Hansch equation from the concept of chemical potential (**Appendix**).

Table 2 Calculated values of median fatal levels (EC_{50}) for several drugs based on a mean relative saturation of 0.006

Drug	*E1%,1 cm (λ nm)*	*Solubility* S *(μg/ml)*	*EC_{50} (calculated) (μg/ml)*
Desipramine	363 (251)	2.1×10^2	13.0
Flurazepam	644 (239)	8.9×10^2	5.3
Nortriptyline	517 (239)	1.2×10^3	7.2

Conclusions

When present at fatal concentrations, many types of drug act as non-specific poisons (so-called Ferguson substances); fatal toxicity is determined only by the relative saturation. This behaviour enables the fatal blood concentrations of other drugs and related compounds to be calculated solely from their solubility in aqueous solution. This approach is only appropriate to compounds which act as central nervous system depressants. However, the majority of drugs associated with fatal poisoning in humans fall into this category.

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Appendix

From a thermodynamic study of equilibria, the following relation can be developed from the differential equations of Gibbs free energy,

$$\mu = \mu^{\circ} + RT \ln(a) \qquad (1)$$

In equation (1), μ is the partial molal free energy (commonly called the chemical potential) of a solute with activity a. The term μ° is the chemical potential of the solute in a suitable standard state. This relation applies to all

solutions but for any substance with a low solubility (a quasi-ideal solution), the activity can be replaced by the ratio C/C_o where C is the actual concentration and C_o is the concentration of a saturated solution.

Equation (1) can therefore be written

$$\mu = \mu^o + RT \ln (C/C_o) \tag{2}$$

If a solute is in equilibrium between two phases (e.g. water and an immiscible solvent), then

$$(C/C_o)_{aq} = (C/C_o)_s$$

Since the partition coefficient is defined as

$$P = (C)_s / (C)_{aq}$$

then equation (2) can be expressed as

$$\mu = \mu^o + RT \ln [P(C)_{aq}/(C_o)_s]$$

which on rearrangement leads to

$$\ln (P) = -\ln(C)_{aq} + \ln (C_o)_s + (\mu - \mu^o)/RT \tag{3}$$

If $(C)_{aq}$ refers to e.g. EC_{50} of a 'Ferguson substance' then, for an homologous series $(\mu - \mu^o)/RT$ is approximately constant, and equation (3) reduces to

$$\log (P) = \log (1/C)_{aq} + \log (C_o)_s + \text{constant} \tag{4}$$

If $(C_o)_s$ is also constant, then equation (4) is equivalent to the empirical Hansch equation.

For the 5,5-disubstituted oxybarbituric acids $(C_o)_s$ is indeed an approximate constant, i.e. the partition coefficients for these substances are inversely related to their aqueous solubilities. The Hansch correlations for fatal blood concentrations of both barbiturates and volatile anaesthetics with P (n-octanol/water) (Moffat & Sullivan, 1981; Stead *et al.*, 1983) are therefore a manifestation of the underlying validity of the Ferguson principle. Even if $(C_o)_s$ is not constant within a series of compounds, but varies in a systematic way with the partition coefficient, then Hansch correlation will still be moderately successful.